Clinical Investigation

Familial Automaticity-Conduction Disorder With Associated Cardiomyopathy

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An unusually large family of European descent was afflicted over four generations by an automaticity and conduction disorder with an associated dilated cardiomyopathy of variable expression. Ten living members affected with the disorder and three presumed affected but dead members were identified. Typically, the disorder presented as a sinoatrial bradyarrhythmia/tachyarrhythmia syndrome, followed by atrial enlargement and, variably, ventricular enlargement and dysfunction. Three family members required pacemaker implantation. Longevity did not seem to be greatly affected, but the demonstrated potential for embolic cerebrovascular events stresses an associated morbidity. The familial incidence was best explained by autosomal dominant inheritance with incomplete penetrance (greater in males and usually occurring first in adolescence) and variable expressivity. The large size of the family, frequency and profile of disease manifestations and disease tracking through at least four generations are unusual features of the familial disease described.

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Many studies, primarily case reports, have appeared in the literature documenting familial conduction system disorders both with[1-6] and without[7-31] associated cardiomyopathy. The abnormalities in these reports, described singly and in combination, have included sinoatrial node dysfunction*; atrial arrhythmias†; atrial standstill[4-6]; a short PR interval[29]; first-, second- and third-degree atrioventricular block‡; atrioventricular dissociation,[11,16,18] and unifascicular, bifascicular or trifascicular block.§

Enlargement of the cardiac silhouette has often been noted, even in the absence of cardiomyopathy, especially when bradycardia is present.[11,12,16,18,24,28-30] This has been attributed to physiologic adaptation due to increased stroke volume and large end-diastolic volumes.[12,16] At times, the distinction between a familial cardiomyopathy with an associated conduction system disorder and benign cardiac enlargement with familial bradycardia has not been clear.[24,30]

Review of reported studies points to variability among families in the patterns of conduction system disorders, inheritance patterns and penetrance and expressivity.[33] Thus, heritability patterns have been variously described as autosomal dominant,[2,23] autosomal dominant with variable penetrance,[17] autosomal dominant with variable expression[22,29,34] and autosomal recessive.[2] Despite the plethora of these reports, most families studied have been small. Pathophysiologic and biochemical mechanisms remain poorly understood and the degree of relatedness of these mechanisms among disorders in different families undefined. Thus, much remains to be learned.

In this article, we present an apparently unique familial syndrome consisting of dysfunction of normal automaticity and conduction, variable degrees of chamber dilatation with cardiomyopathy and valvular prolapse in members of four generations of one large family.

Patients and Methods

The current report concerns the "V" family, a large kindred of European extraction living for more than four generations in a relatively circumscribed geographic area in the western United States.

*References 2, 3, 6, 12, 13, 16, 18-21, 24-26, 30,31.
†References 2-7, 10, 12, 13, 15, 18, 19, 23, 24, 27, 30.
‡References 1, 3, 5-7, 11, 13, 17, 18, 20, 22-24, 30, 32
§References 2, 3, 5, 9, 13, 14, 17, 20, 22-24, 30, 32

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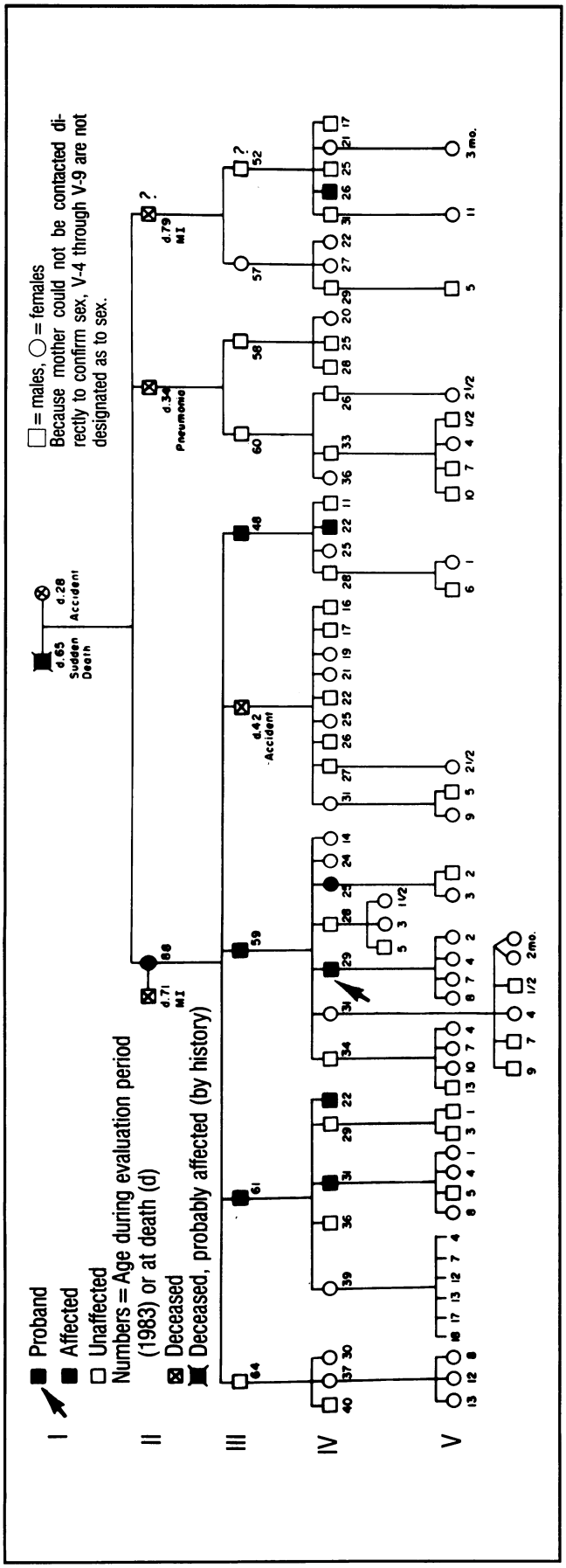


Figure 1.—Family tree of the "V" kindred.

ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
HLA = human leukocyte antigen

The investigation began with a thorough evaluation of the proband, including history, physical examination, review of medical records, electrocardiography, laboratory blood testing—including a biochemistry panel, complete blood count, thyroid function studies, antinuclear antibody and rheumatoid factor titers, catecholamine levels, blood and tissue (human leukocyte antigen [HLA]) typing—cardiac catheterization and myocardial biopsy.

After a family history showed the probable involvement of the 29-year-old male proband's sister, father and paternal grandmother, further evaluation of all descendants of the paternal grandmother was undertaken. We were able to interview directly 40 family members. Questionnaires were directed at cardiovascular symptoms, past medical and family history and review of systems. Information on family members not seen was elicited from other family members, by telephone and from personal physicians. Physician and hospital records were available and reviewed in 15 instances. Electrocardiograms (ECGs) were obtained on 47 members. All available, previously done ECGs were also reviewed. Echocardiograms were obtained on 39 members. HLA typing was carried out on 28 members. Serum iron studies were done on two, cardiac catheterization and endomyocardial biopsy on three and electrophysiologic studies on one.

All current echocardiograms and ECGs were recorded during the period June 1983 to December 1983. Studies were obtained on all members for whom travel to the hospital was not prohibitive. Because the familial pattern seemed to be one of onset during late childhood (puberty) or young adulthood, only a portion (nine young members) of the fifth generation was evaluated.

The familial conduction system disorder was considered to be present if sinoatrial node dysfunction, atrial arrhythmia or both were documented by ECG. Pathologic sinus bradycardia was considered if the resting heart rate was less than 50 beats per minute and associated with other evidence of disease (pauses longer than two seconds, junctional escape rhythms, tachyarrhythmias or a combination or all of these). Evidence for cardiomyopathy was defined echocardiographically by chamber dilatation, especially when accompanied by systolic dysfunction, or a suggestion of elevated right-sided heart filling pressures based on abnormal echocardiographic dynamics of the inferior vena cava.[35] Echocardiograms (both single and two-dimensional modes) were read blinded. HLA typing was done using a Microwell cytotoxicity assay.[36]

Results

Family "V"

Proband. The male proband (Figure 1, case IV-11) presented at age 29 with residual neurologic deficits from a recent cerebrovascular accident attributed to embolism of a left atrial thrombus during atrial fibrillation. He showed the

tachycardia/bradycardia variant of sinoatrial conduction disease ("sick sinus syndrome"). Earlier evaluation at age 17 showed a junctional rhythm, with a rate of 55 beats per minute, increasing to only 60 beats per minute with vigorous exercise (Figure 2). Symptomatic paroxysms of atrial fibrillation were also observed, recurring at intervals of days to months, for which he was treated with digoxin or β-blockers. Normal blood chemistry and thyroid function values, negative rheumatoid factor and antinuclear antibody titers, normal plasma norepinephrine, epinephrine and dopamine levels and normal arterial blood gas measurements were found. A chest x-ray film (Figure 3) showed a globular, enlarged heart. An

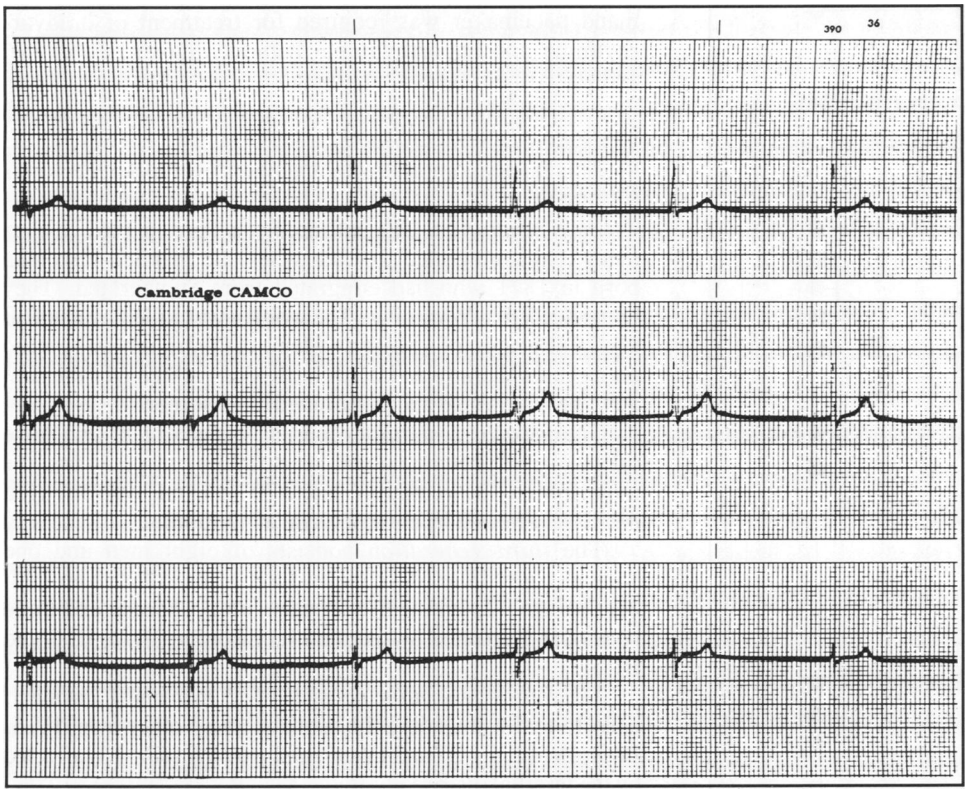


Figure 2.—Electrocardiographic strips show a slow junctional rhythm, typical of findings in an affected young adult, such as IV-8, IV-11. Leads I, II and V_1, top to bottom, are shown.

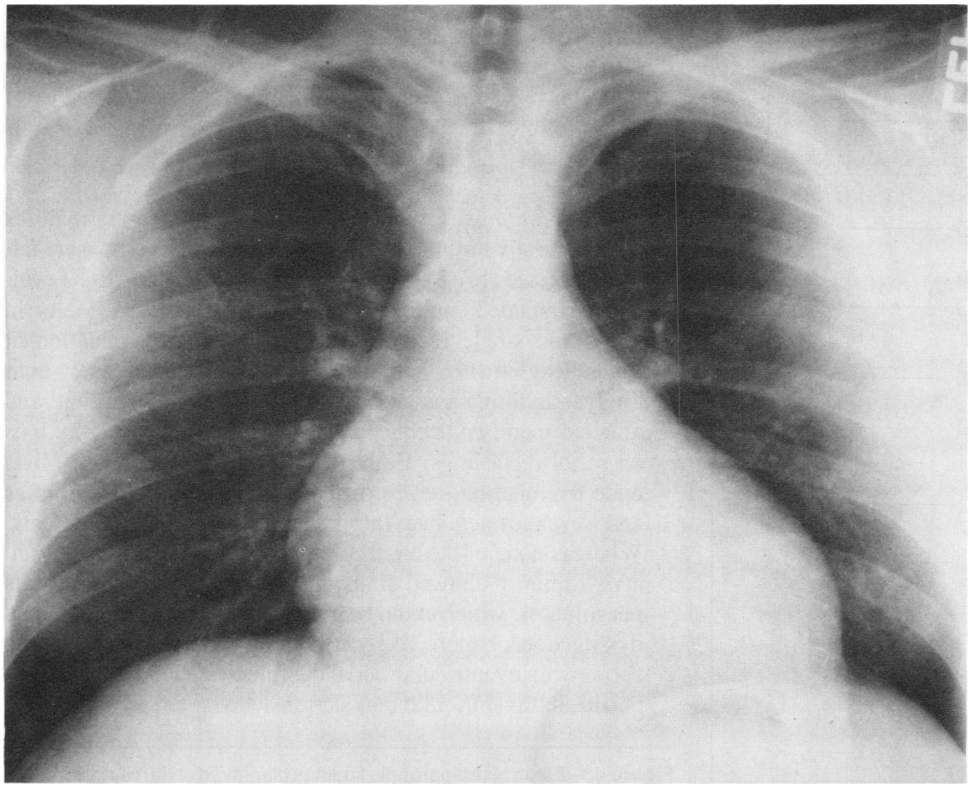
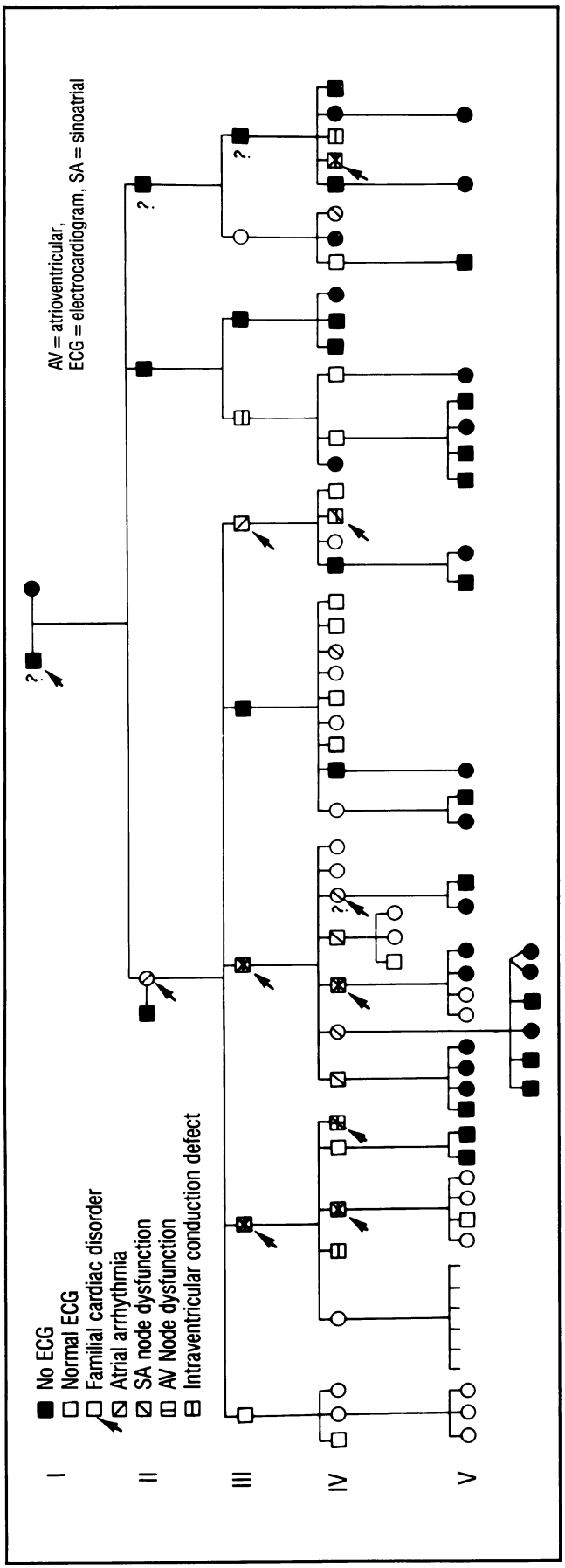


Figure 3.—A chest x-ray film of the propositus, IV-11, shows a globular, enlarged heart shadow.



echocardiogram showed four-chamber cardiomegaly, mitral valve prolapse and probable tricuspid valve prolapse. A heart catheterization showed a grossly dilated right side of the heart. Filling pressures were elevated with a right atrial mean of 10 to 12 mm of mercury and a pulmonary arterial capillary mean of 10 to 15 mm of mercury. A myocardial biopsy specimen was unrevealing except to exclude myocarditis. A demand pacemaker was required for treatment of bradyarrhythmia and antiarrhythmic therapy (digoxin, quinidine) and warfarin for tachyarrhythmia.

Overview of Family History

This family comprises 103 members over five generations (Figure 1).

First generation. The patriarch was born in 1862 in Germany and immigrated to Utah where he married a woman born in 1871 who had emigrated from Switzerland. They homesteaded in Wyoming. The woman was killed by a bull at age 28. Because of a heart problem, the patriarch was placed on digitalis therapy and died in his sleep at age 64. Presumably, he manifested and transmitted the disorder.

The *second generation* consists of two men who have died—one of pneumonia and heart failure at age 34 and the other from a "heart attack" at age 79—and one woman, aged 88 (II-1), affected by chronic atrial arrhythmias.

The *third generation* consists of eight men and one woman, ages 48 to 64 years, including one killed in an accident at age 42, one with coronary artery disease and three sons of II-1 affected by the familial disorder (III-2, III-3 and III-5).

The *fourth generation* consists of 25 men and 17 women, ages 11 to 40, including the proband and 4 other men (IV-6, IV-8, IV-11, IV-27 and IV-39) and 1 woman (IV-13) affected by the familial disease.

The *fifth generation* consists of 47 children, ages 2 months to 18 years, 1 with William's syndrome (supravalvular aortic stenosis), unrelated to family "V" disorder. The disorder has not yet been confirmed in this generation, probably because of its young age.

Special Studies

ECG findings (Figure 4, Table 1). Rhythm abnormalities are essentially limited to the ten living members who were felt to be affected (n = 8) or probably affected (n = 2). ECG evaluation included multiple recordings over several years in seven and single ECGs at the time of study evaluation in three. Rhythm findings were complex; in most cases, both bradyarrhythmia and tachyarrhythmia had been present, and affected members frequently had several abnormal rhythms on serial recordings. Eight of the ten had evidence of sinus node dysfunction, seven of ten had atrial tachyarrhythmias and seven of ten had intraventricular conduction defects. Whereas none of the other 37 members with ECGs had atrial arrhythmia, 6 showed sinus bradycardia (less than 60 beats per minute), which could be evidence of early sinoatrial node dysfunction or more likely a normal variant. None of these showed atrioventricular nodal dysfunction, but three had borderline intraventricular conduction delay.

Figure 4.—Electrocardiographic findings displayed on family tree.

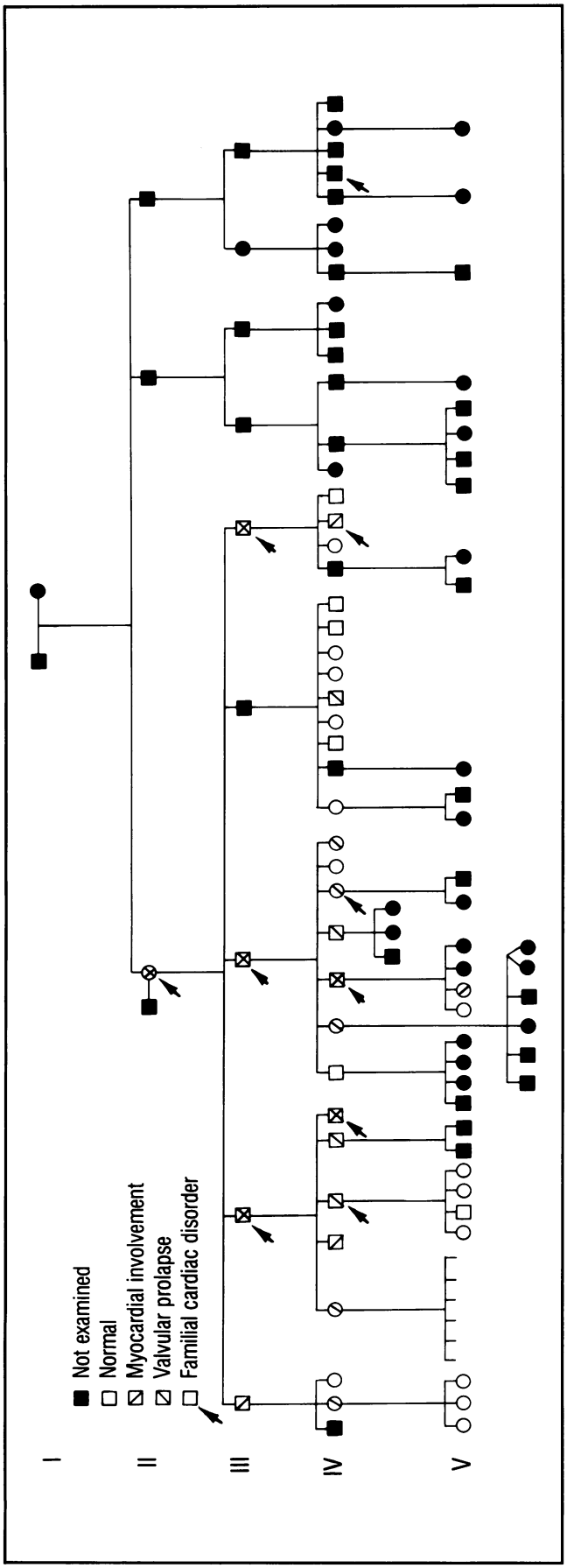


TABLE 1.—*Electrocardiographic (ECG) Findings**

ECG Abnormalities	Generation: II	III	IV	V	Total
No. Tested:	1	6	30	9	46
Atrial Arrhythmias					
Atrial tachycardia	...	2	2	...	4
Atrial fibrillation	1	3	...	...	4
Atrial flutter	...	2	2	...	4
SA Node Findings					
Sinus arrhythmia†	...	...	17	4	21
Sinus bradycardia†	...	...	7	1	8
Sinus pauses	...	...	2	...	2
Junctional rhythm	...	2	3	...	5
AV Node Dysfunction					
1° AV block	...	...	3	...	3
2° AV block	...	...	0	...	0
3° AV block	...	...	0	...	0
Permanent Pacemaker	...	...	3	...	3
His/Purkinje System Dysfunction					
IVCD	...	...	4	...	4
RBBB	...	2	2	...	4
LBBB	...	1	...	...	1
LAH	...	1	1	...	2
Miscellaneous					
RAD†	...	...	8	2	10
Juvenile pattern†	...	...	4	4	8
LVH/voltage ± ST-TΔ†	1	1	3	6	11
ST-T changes	1	4	2	...	7
High J point†	...	1	10	3	14
Peaked T waves†	...	1	8	...	9
PVC	...	3	...	...	3

AV = atrioventricular, IVCD = intraventricular conduction delay, LAH = left anterior hemiblock, LBBB = left bundle branch block, LVH = left ventricular hypertrophy, PVC = premature ventricular complex, RAD = right axis deviation, RBBB = right bundle branch block, ST-TΔ = [secondary] ST segment and T-wave changes, 1° = first degree, 2° = second degree, 3° = third degree

*A patient may have more than one finding.
†May not always represent abnormality, especially in juvenile pattern.

Two members of the third and three of the fourth generation had documented junctional rhythms; two of the fourth had sinus pauses. First-degree atrioventricular block, probably reflecting atrioventricular node dysfunction, was observed in three of the fourth generation. Atrial tachycardia was found in four members of the third (n = 2) or fourth (n = 2) generations, atrial fibrillation in four of the second (n = 1) or third (n = 3) generations and atrial flutter in four of the third (n = 2) or fourth (n = 2) generations. Right bundle branch block was found in four of the third (n = 2) or fourth (n = 2) generations. Left anterior divisional block was found in two (third generation, 1; fourth, 1) and complete left bundle branch block in one (third generation). Other intraventricular conduction variants were noted in four. Three members of the fourth generation have permanent pacemakers (IV-8, IV-11, IV-39).

Echocardiography. Findings in 38 echocardiographic studies included myocardial abnormalities (chamber enlargement, dysfunction) in 6 and valvular abnormalities (prolapse) in all 9 affected members studied (Figure 5, Table 2). Myocardial abnormality appeared to be greater with increasing age of members, affecting atria, then the right ventricle, then (variably) the left ventricle. Five affected persons showed

Figure 5.—Echocardiographic findings displayed on family tree.

enlargement of both atria and the right ventricle, the pattern most typical of the familial cardiomyopathy; a variable degree of valvular prolapse was also present. In two members (third generation), moderate left ventricular enlargement and dysfunction have also developed. Nine other members (fourth generation) have valvular closure variants or prolapse; three of these have manifested or suspected familial "V" disease. Because closure variants or minor degrees of prolapse may be commonly seen in the general population (an incidence of about 20%, especially in women),[37] this finding may be too nonspecific to be an early diagnostic marker of the familial disorder.

HLA typing. Histocompatibility testing for the HLA-A, -B and -C loci, located on chromosome 6,[36] were determined for case II-1 and 26 of her descendants older than 16 years. No linkage could be established between HLA type and the familial disorder. Also, no linkage with ABO blood groups was found.

TABLE 2.—*Echocardiographic Chamber Enlargement*

Findings	Generation: II	III	IV	V	Total
	No. Tested: 1	4	24	9	38
Chamber Enlargement*					
Right atrium	1	3	4†	...	8‡
Right ventricle	1	3	3	...	7§
Left atrium	1	3	2	...	6‖
Left ventricle	...	2	1	...	3¶
Valvular prolapse	1	3	9	...	13#

*Patients could have more than one chamber enlarged.
†Abnormal inferior vena caval dynamics in 1 other, suggesting increased right atrial pressure.
‡4-Chamber area (n = 7): 35.3 ± 9.5 cm^2 (22 to 46 cm^2), nl < 18 cm^2.
§Short axis dimension (n = 6): 47.2 ± 4.3 cm.
‖ 4-Chamber area (n = 6): 37.7 ± 8.8 cm^2 (22 to 48 cm^2), nl < 18 cm^2.
¶End-diastolic dimension (n = 3): 62.0 ± 3.0 cm (59 to 65 cm), nl < 56 mm.
#Prolapse borderline (mild) in 6, mitral prolapse = 12, tricuspid prolapse = 5, aortic prolapse = 1.

Case Studies

Case II-1. This 88-year-old matriarch has had irregular heart action associated with dyspnea and weakness since her early 20s. A heart murmur has been noted for more than 40 years. ECGs from 1971 have shown atrial fibrillation, for which she was given digitalis. Treatment has recently been instituted for hypertension and heart failure. Echocardiography shows pronounced biatrial enlargement, left ventricular hypertrophy without substantial dilatation, mild right ventricular enlargement and mild mitral and tricuspid valve prolapse.

Case III-2. This 61-year-old second son of II-1 began having palpitations and exertional dyspnea at age 17. Tachycardia—for which he was treated with digitalis—and a "large heart" were diagnosed at age 18 when a transient ischemic attack occurred. A cerebrovascular accident with aphasia and right-sided weakness occurred at age 37, and warfarin therapy was begun. Heart failure developed at age 54, associated with a slow junctional rhythm (45 beats per minute), and furosemide was added to the treatment regimen. Atrial flutter-fibrillation was recorded on an ECG in 1942—together with radiographic cardiomegaly—and again in 1959. Atrial tachycardia with variable block, slow junctional rhythms, atrial flutter with 4:1 block and left axis deviation have all been noted at times since 1977 and left bundle branch block since 1983. Echocardiography shows four-chamber cardiomegaly with depressed left ventricular function (Figure 6) and borderline mitral and tricuspid valve prolapse.

Case III-3. This 59-year-old third son of II-1 noted the onset of a fast, irregular heartbeat at age 13, associated with dizziness, dyspnea and fatigue and exacerbated by exercise. He was disqualified from military induction at age 20 because of arrhythmia and a heart murmur. ECGs dating from 1955 have shown atrial fibrillation with a right bundle branch block aberration. Symptomatic paroxysms of atrial fibrillation, for which he has been treated intermittently with digitalis, quinidine and propranolol hydrochloride, recurred frequently between ages 20 and 50. Heart failure appeared in 1977; the propranolol therapy was stopped and a regimen of furosemide begun. Additional arrhythmias, recorded on ECGs since

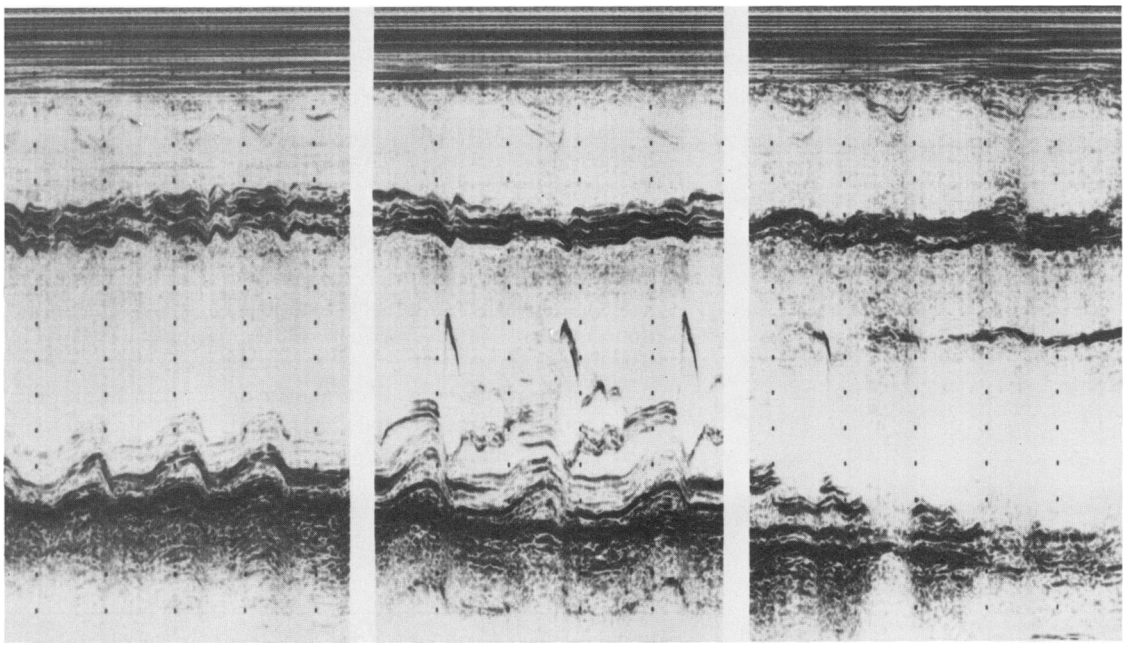


Figure 6.—Composite echocardiographic M-mode sweep, patient III-2, showing moderate multichamber cardiac enlargement (left atrium, left ventricle and right ventricle shown).

1958, have included junctional rhythms (44 to 71 beats per minute), atrial tachycardias with 1:1 (200 beats per minute) and 2:1 block (100 beats per minute) and atrial flutter, usually with 4:1 block (Figure 7). Echocardiography shows four-chamber cardiomegaly and mitral valve prolapse.

Case III-5. The fifth son of II-1, aged 48 years, first experienced fast irregular heart action at age 13, associated with dyspnea, lightheadedness and chest pain. Cardiologic evaluation confirmed an abnormal (irregular) rhythm and a heart murmur. Episodes of tachyarrhythmia occurred paroxysmally (three to four per week) until age 30, then became constant. Therapy has included digitalis, β-blockage and warfarin. Electrocardiography shows atrial flutter with a slow ventricular response and digitalis effect; an echocardiogram shows biatrial and right ventricular enlargement, prolapse of mitral, aortic and tricuspid valves and an aneurysm of the interatrial septum.

Case IV-6. This 31-year-old third son of III-2 presented to medical attention at age 23 after a four-day episode of rapid heart action associated with palpitation, dizziness, fatigue and brief chest pain. An ECG showed atrial flutter with variable block and incomplete right bundle branch block. He had conversion to sinus bradycardia with first-degree block after treatment with digitalis. Paroxysmal atrial flutter or fibrillation, lasting for several hours, has recurred every few months, especially during periods of stress. A current ECG shows sinus arrhythmia and first-degree block with incomplete right bundle branch block; an echocardiogram shows no abnormalities.

Case IV-8. The fifth child of III-2 has noted bradycardia for years but recently presented at age 22 with dizzy spells three to four times a week. ECGs showed junctional rhythm with rates of 36 to 44 beats per minute, with atrial ectopic beats. A Holter monitor, however, showed episodes of sinus arrest, with pauses of as long as 5.6 seconds (Figure 8). An echocardiogram showed mild biatrial and right ventricular enlargement and anterior mitral leaflet prolapse. Catheterization was done and a permanent ventricular pacemaker placed. A cardiac biopsy specimen showed nonspecific changes: mild edema, myofibrillary loss and degenerative change. Serum iron values were normal. An electrophysiologic study showed absent atrial activity, increased atrial and ventricular capture thresholds, a normal ventricular effective refractory period (230 ms) and mildly increased filling pressure (right atrial mean, 12 mm of mercury; pulmonary arterial capillary mean, 14 mm of mercury).

Case IV-13. This 25-year-old daughter of III-3 first noted lightheadedness, dizziness and exertional dyspnea at age 19. ECGs over six years have shown sinus arrhythmia and bradycardia, with rates of 36 to 70 beats per minute. Prolapse of the anterior mitral leaflet has been noted on echocardiography. "Heart skips" occur with exercise, but no tachyarrhythmias have yet been documented.

Case IV-27. This 22-year-old son of III-5 has had rapid but regular palpitations after exercise for six years. Sinus arrhythmia and bradycardia (to 45 beats per minute) have been recorded. Echocardiography shows slight right ventricular enlargement. His present findings are also suspicious of the disorder.

Case IV-39. This 26-year-old grandnephew of II-1 exhibits features of the familial disorder. Sinus bradycardia (50 to 60 beats per minute) and first-degree atrioventricular block were first noted at age 11. Subsequently, both bradyarrhythmias and tachyarrhythmias were documented, for which he was later treated with a permanent pacemaker (age 20) and drugs. ECGs at age 13 showed junctional rhythm, 23 to 54 beats per minute and atrial tachycardia (rate 200) with variable but relatively slow ventricular response (50 to 70 beats per minute). An ECG at age 20 showed atrial flutter with 4:1 block, right axis deviation and incomplete right bundle branch block. Radiographic cardiomegaly has been present since 1968. A heart biopsy specimen in 1971 showed no abnormalities by light microscopy.

Discussion

Summary of Features of Family "V" Disease

The five generations of family "V" were found to have a conduction system disorder traced through four generations; members of the fifth generation are still too young (aged less than 13 years) to evaluate disease expression. Presentation is typified by the onset at ages 10 to 20 of sinoatrial dysfunction. Most commonly, pronounced sinus bradycardia is followed by intermittent sinus arrest and junctional escape rhythms, then atrial fibrillation, atrial flutter and sometimes atrial

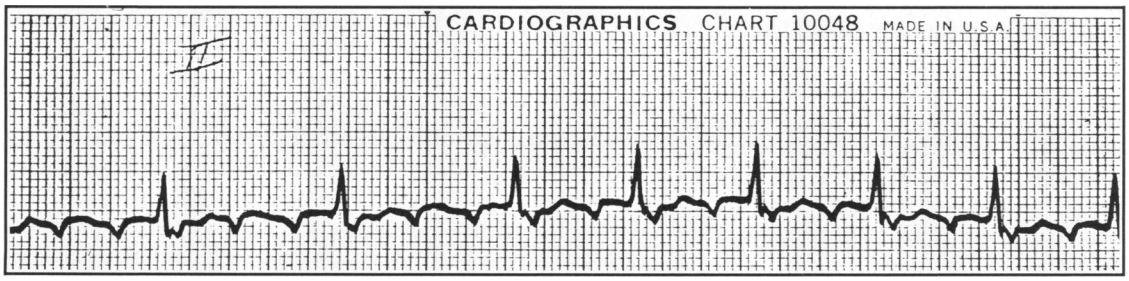


Figure 7.—Slow atrial flutter with variable block, one of many rhythms in patient III-3 (retouched).

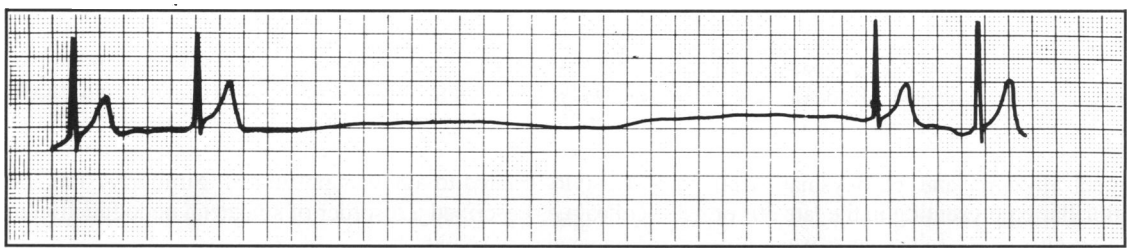


Figure 8.—A Holter electrocardiographic rhythm strip in patient IV-8 shows a sinus pause of 5.6 seconds (retouched).

tachycardia (usually with block). Tachyarrhythmias may represent escape rhythms or additional pathology; probably both possibilities apply to family "V." This disorder of automaticity and conduction is similar to an early form of the sick sinus syndrome, which includes bradycardia, tachycardia and brady/tachycardia variants.[38] First-degree block and (usually later) intraventricular conduction delay in several, however, suggest additional involvement of the atrioventricular node and the His-Purkinje system. The age distribution of findings suggests that the conduction disease generally precedes cardiac chamber enlargement, which involves the atria early on, then the right ventricle and variably the left ventricle. Because echocardiographic observations are cross-sectional rather than serial, the temporal progression in myocardial involvement should be viewed as tentative. (Valvular prolapse, generally mild, was an associated finding but appears to be nonspecific, occurring in otherwise unaffected members [fourth generation]).

Adverse sequelae of family "V" disease, in addition to symptoms of the arrhythmias, include the possible need of a permanent pacemaker, the possibility of arterial embolic events at a young age and congestive heart failure after the fifth decade. However, substantially decreased survival (as a result of early sudden death or end-stage heart failure) before age 60 does not appear to be a characteristic of this disorder.

Heredity and Nature of the Disorder

The observed inheritance pattern is consistent with an autosomal dominant trait with incomplete penetrance and variable expression. The age of clinical onset is typically 10 to 20 years, with earlier and more complete penetrance in men than in women: 8/14 at-risk men (based on parental expression) with historical or ECG evaluation have manifested the disorder (8/23 of all men) versus 2/8 at-risk women (2/7 older than 20 years, 2/15 of all women).

The nature and site of the abnormal genetic locus is unknown but is not linked to blood groups or to the HLA loci on chromosome 6.[36,39] Limited pathologic evaluation (biopsy material) in three affected younger members has been unrevealing except to exclude myocarditis or gross myocardial pathology.

Several causes of familial disorders with features overlapping those described here have been suggested, including chronically increased vagal tone[28]; genetically determined sinoatrial node, atrioventricular node and His-Purkinje system degeneration (compare Friedreich's ataxia, Marfan's syndrome, progressive muscular dystrophy, primary pulmonary hypertension),[19] or a genetically determined conduction and contractile myofiber degeneration due to a metabolic defect or microvascular insufficiency. An associated defect in connective tissue causing valvular prolapse must also be considered.[37]

Comparison With Literature Cases

The features of family "V" disease may be compared with those reported in pertinent articles in the past decade or two.

Bacos and co-workers described a family of nine members, representing three generations, who had congenital atrioventricular junctional rhythms and paroxysmal atrial tachycardia and atrial fibrillation presenting in the late 20s or early 30s, later becoming chronic.[12] Inheritance was autosomal dominant. Chest x-ray films showed moderate cardiomegaly, but right-sided heart pressures were normal. Echocardiographic and histologic evaluations were not done.

Spellberg presented a family with sinoatrial node dysfunction manifested primarily in adulthood by sinus arrest with atrioventricular nodal or ventricular escape rhythms.[19] Seven members of three generations, ages 13 to 68, were affected. Syncopal episodes occurred, associated with both bradycardia and runs of supraventricular tachycardia. Chronic atrial tachyarrhythmia—that is, atrial fibrillation—as an eventual maintenance rhythm and myocardial involvement were not described, however.

Livesley and associates described a father and 13-year-old son with prominent sinus bradycardia (to 42 beats per minute) and first-degree atrioventricular block.[21] Two other children had sinus bradyarrhythmia after Valsalva maneuvers, suggesting an autosomal dominant pattern. Progression of this mild conduction disorder was not described.

Williams and colleagues studied 20 members of two generations of a family with conduction abnormalities and atrial myopathy.[6] Sinus bradycardia, first-degree atrioventricular block, supraventricular tachycardias and, finally, stable junctional bradycardias were noted. Right atrial pacing was unsuccessful in one, in whom ventricular pacing was required. These findings were attributed to a cardiomyopathy involving the atria and supraventricular conduction system.

Waxman and colleagues described familial atrioventricular block with sinus and atrioventricular node dysfunction in 5 of 28 members of a family spanning four generations.[24] All five had cardiomegaly, but only one had heart failure. Progression of the disorder was not uniform but was manifested by sinus bradycardia, atrial fibrillation, complete atrioventricular block and intraventricular conduction delay. Episodes of ventricular tachycardia were observed in three. In the one autopsied case, fibrosis of the sinoatrial and atrioventricular nodes and proximal His bundle were observed with sparing of cardiac muscle. Inheritance appeared to be autosomal dominant with incomplete penetrance. The ages of affected members were 50 to 70 years at diagnosis.

Caralis and Varghese described six of nine family members (ages 3 and older) over three generations with sinus bradycardia (38 to 40 beats per minute) and escape junctional rhythms associated with lightheadedness and occasional syncope.[28] Minimal cardiomegaly and no heart failure were present. A persistent increase in vagal tone was one postulated mechanism of sinoatrial node dysfunction.

Nordenberg and co-workers presented two siblings with syncope at ages 12 and 17 associated with sinoatrial node dysfunction with sinus bradycardia, sinus pauses and sinus arrest.[26] A permanent pacemaker was required in one and an embolic stroke occurred in the other (age 23).

Jacovella and associates reported electrophysiologic studies in three siblings with a familial sinoatrial node disorder, two of whom required a pacemaker.[27] Three additional members of the family (of 24 evaluated) had atrial or ventricular arrhythmias. Autosomal dominant transmission with expressivity related to age was postulated. Similarly, Tan and colleagues described a disorder of sinoatrial node function in a father and two children.[31]

Conclusion

Although many families have been described over the past two decades with sinoatrial node dysfunction and varying degrees of atrioventricular node and His-Purkinje disease that can be compared with the present family study, the size of the "V" kindred, the temporal span of the observations (four to five generations), the complex and variable rhythm features and the more complete assessment of laboratory and myocardial abnormalities (echocardiographically and invasively) are of unusual interest in the familial "V" disease of automaticity and conduction with associated mild cardiomyopathy. Future additional observations to further define the pathophysiology and biochemistry of the disorder will be of interest.

Addendum

Since submission of this manuscript, patient III-2 (age 61) has died of a refractory ventricular tachyarrhythmia. Postmortem examination showed four-chamber cardiomegaly, with advanced and diffuse histologic degenerative changes throughout both the conduction system and myocardium. Changes included cell hypertrophy with nuclear enlargement and atypia, vacuolization and degeneration with cell dropout and fibrosis and focal myocarditis. These changes were those of an idiopathic cardiomyopathy and were nonspecific. Special stains were not revealing.

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